REMARKS

I. PENDING CLAIMS AND SUPPORT FOR AMENDMENTS

Upon entry of the present amendment, claims 27, 29, 30, 36-38, and 57-95 will be pending in this application. Claims 57-92 have been withdrawn from consideration as being directed to a nonelected invention. As a result, claims 27, 29, 30, 36-38, and 93-95 are before the Examiner on the merits.

Applicants have amended claim 27 to recite the fatty acyl groups recited in claims 32 and 33. This is clearly supported in original claims 3 and 4, as well as at various locations in the specification. Applicants have also added new claim 95, directed to compounds wherein both fatty acyl moieties are EPA. Support for this claim can be found in the specification at page 17. No new matter has been added.

II. FINALITY OF OFFICE ACTION

Although the summary page of the Office action indicates that the action is final, the body of the Office action does not so indicate. Moreover, a final Office action would not be proper or appropriate given the new grounds of rejection made therein. Applicants confirmed with the Examiner by telephonic interview on February 2, 2000 that the indication of finality on the summary page was inadvertent, and that the action was not made final. Based upon this assertion, Applicants have not filed a Notice of Appeal with this response, since such a filing is unnecessary to maintain pendency, irrespective of the disposition of the application as a result of this response.

III. THE PRESENT INVENTION

The presently claimed invention relates to biologically active compounds that use a 1,3-propanediol as a linking moiety between fatty acid moieties that are esterified with the diol hydroxy moieties. This choice of linking moiety is particularly advantageous because it is well tolerated by the body, and provides a convenient delivery system for bioactive fatty acids. In particular, the 1,3-propanediol linking moiety can be thought of as a deoxyglycerol moiety, which Applicants have found to be sufficiently similar in structure to glycerol to be well tolerated by the body. The 1,3-propanediol also does not contain a chiral center, which would be present in a substituted glycerol. This eliminates the formation of multiple optical isomers, during synthesis, rendering synthesis and purification of the compounds considerably less complicated. In addition, problems of acyl migration, described at page 11 of the specification, are avoided.

As described in the specification at pages 9-11, these bioactive fatty acids perform important roles in body metabolism, have therapeutic effects on brain function (indeed, it is estimated that some 30% of the dry matter of the brain consists of fatty acids), and are useful in the treatment of cardiovascular disease, the treatment of inflammation, the treatment of osteoporosis, the treatment of cachexia, and the treatment of other disease conditions. In particular, treatment with fatty acids that are metabolites of the n-6 and n-3 series of fatty acids is of particular interest, since it has been found that simply supplying the body with precursors of these metabolites does not provide adequate therapy, particularly where the disease condition results from or is typically accompanied by problems with metabolism. In these situations, it is desirable to supply more than one of these metabolites at once, and the

compounds of the present invention are designed to do this without the problems that accompany the use of glycerides. For example, the compounds of the present invention are considerably easier to synthesize with high specificity than are the corresponding glycerides.

IV. THE REJECTIONS UNDER 35 U.S.C. § 112

At page 3 of the Office action, the Examiner has rejected claims 27-56 under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection and request reconsideration and withdrawal thereof.

The Examiner has objected to a number of different terms appearing in the claims, including the terms "residue," "nutrient," "drug," "derivative," etc. While Applicants do not agree with the Examiner's characterization of these terms as indefinite, particularly when the terms are read in context with the remainder of the claims and in light of the specification, Applicants submit that the Examiner's rejection is moot because none of the claims presently before the Examiner on the merits uses any of the terms mentioned in the rejection. Accordingly, the Examiner's rejection should be withdrawn.

V. ANTICIPATION REJECTIONS

A. Claims 27-29

At page 3 of the Office action, the Examiner has rejected claims 27-29 under 35 U.S.C. § 102(b) as being anticipated by Barsky et al. (U.S. Patent No. 2,924,528), or Alsop et al. (U.S. Patent No. 2,993,063), or by British patent publications 1,493,098, or 1,529,062, or 2,161,477, or by European publication 116,114, or by Japanese publication 57-067,511, or by

Breusch et al. (Chemische Berichte, vol. 88, pp 1511-1519 (1955)). Applicants respectfully traverse this rejection, and request reconsideration and withdrawal thereof.

While Applicants do not agree that any of the cited references anticipate unamended claims 27-29, Applicants submit that none of the cited references anticipates the presently amended claims, as evidenced by the failure of the Examiner to reject either claim 32 or 33 over any of the cited references. Accordingly, the Examiner's rejection should be withdrawn.

B. Claims 27-33 and 35

At page 3 of the Office action, the Examiner has rejected claims 27-33 and 35 under 35 U.S.C. § 102(b) as anticipated by British patent publication 1,529,062 (which Applicants assume should be 1,529,762), or European patents 056,189, or 222,155, or 393,920. Applicants respectfully traverse the rejection and request reconsideration and withdrawal thereof.

GB 1,529,762 does not anticipate the claims because the only propanediol derivatives specifically disclosed are oleoyl (stearoyl-4-hydroxybutyryl) propylene glycol and 1-behenoyl-2-oleoyl propylene glycol. Neither of these compounds falls within the scope of the present claims, which are directed to 1,3-propanediol esters with acid moieties completely different from those disclosed in the cited reference.

EP 056,189 does not anticipate the claims because it is limited to disclosure of 2,3-butanediol compounds. The present claims clearly state that they are drawn to 1,3-propandiol derivatives.

EP 222,155 does not anticipate the claims because it is limited to disclosure of 5-fluorouracil derivatives. The present claims do not read on 5-fluorouracil derivatives.

EP 393,920 does not anticipate the claims because it is limited to disclosure of nucleoside antiviral compounds. The present claims do not read on compounds having nucleoside moieties.

VI. OBVIOUSNESS REJECTIONS

A. Claims 27-29, 32, 33, 36-38, 93, and 94

At pages 3-4 of the Office action, the Examiner has rejected claims 27-29, 32, 33, 36-38, 93, and 94 under 35 U.S.C. § 103(a) as obvious over Barsky et al.; or Alsop et al.; or Goldblatt et al.; or British patent publication nos. 1,293,277, 1,493,098, 1,529,762, 1,356,197, or 2,167,477; or European patent publication nos. 056,189, or 161,114, or 246,540, or 405,873, or Breusch et al. Applicants respectfully traverse this rejection and request reconsideration and withdrawal thereof.

Applicants assume that the Examiner is asserting that each of the fifteen (15) references individually renders obvious each claim, since there is no indication in the rejection that reference teachings are being combined.

As described above and in the specification, Applicants have found that the 1,3-propanediol linkage between fatty acids is a particularly important feature of the invention.

Barsky et al. is directed to edible fat substitute compositions that contain esters of two or more very specific saturated fatty acids: palmitic and stearic acid. There is no teaching or suggestion that these acid moieties can or should be varied from these acids, or that

unsaturated acids could be used, or that the result would be an edible composition. Moreover, there is no teaching or suggestion to modify the 1,2-substituted propane compounds disclosed in Barsky et al. to 1,3-substituted propane compounds. For these reasons, the Examiner has failed to establish a *prima facie* case of obviousness.

Even assuming, *arguendo*, that such a modification were structurally obvious, there is no suggestion in Barsky et al. that such esters would have the therapeutic uses disclosed in the present application for the claimed compounds. Accordingly, any conclusion of obviousness is rebutted by the unexpectedly different results obtained with the present invention, namely therapeutic utility.

Similar arguments apply to Alsop et al., Goldblatt et al., and British patent publication no. 1,493,098 (which discloses alkylene glycol esters used as solvents and plasticizers, not as therapeutic agents),

Klemann et al. also relates to edible fat substitutes that contain fatty acid diesters of dihydric alcohols. However, the dihydric alcohols of Klemann et al. all require at least four carbon atoms, many of which contain 1,2-diol substitution or unsaturation. Applicants' claims are specific to 1,3-substituted propane diols, provide an easily synthesizable, therapeutically acceptable "deoxyglycerol" linking group as explained above. The unsaturated, longer chain diols disclosed in Klemann et al. do not provide such a linking moiety. Moreover, there is no suggestion in Klemann et al. to modify the diol moiety to contain fewer than the four carbon minimum that Klemann et al. disclose. Accordingly,

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness over Klemann et al.

British patent publication no. 1,293,277 relates to lubricant compositions containing mixed esters of 2,2-dimethylpropane-1,3-diol. Neither the acid moieties nor the diol moiety disclosed in this publication are even close to those claimed in the present application. Moreover, there is no motivation in the '277 publication to modify the acid or diol moieties disclosed therein so substantially as to obtain the claimed invention with any reasonable expectation that the resulting compounds would possess the lubricant properties required by the '277 publication.

The disclosure of British patent publication no. 1,529,762 has been discussed above. As explained above, the '762 publication contains disclosure limited to esters having acid moieties that are structurally very different from the acid moieties recited in the present claims. These are not simply homologs, and a worker of ordinary skill in this art would not have been motivated to substantially modify the propylene glycol compounds described in this publication sufficiently drastically to obtain the structures of the compounds of the present invention.

British patent publication no. 1,556,197 relates to brominated flameproofing agents. The present claims do not read on brominated esters, and one of ordinary skill in the art would not have been motivated to remove the bromine from the compounds disclosed in the '197 publication, since doing so would clearly destroy or significantly diminish their flame retardant properties.

British patent publication no. 2,161,477 and European publication 161,114 relate to plant growth regulant compositions. While a di-linolenic acid ester of 1,3-propanediol is disclosed, this linolenic acid is the n-3 series alpha-linolenic acid, and not the n-6 series gamma-linolenic acid recited in the claims.

The term "linolenic acid" as used in these publications refers to the alpha-linolenic acid, as evidenced by the attached page from Lehninger, Principles of Biochemistry, 1982, p. 305. Table 12-2 designates as "linolenic acid" the delta-9,12,15 acid (i.e., alpha-linolenic acid), rather than the delta-6,9,12 acid (i.e., gamma-linolenic acid).

The gamma-linolenic acid compounds recited in the claims are particularly closely related to the fatty acids in lipid barriers in the human body. Gamma-linolenic acid is beyond the delta-6-desaturase conversion of fatty acids in the body, while alpha-linolenic acid is not (see Figure 1, at page 7 of the specification). Thus, a worker having ordinary skill in this art would not have been motivated to replace the alpha-linolenic acid esters disclosed in the '477 publication with gamma-linolenic acid esters with any reasonable expectation that the gamma linolenic acid esters would function as plant growth regulants.

European publication no. 056,189 relates to 2,3-butanediol diesters used as antiulcer treatments. As described above, the present invention relates to diesters of specific carboxylic acids wherein the acid moieties are linked by a specific diol linking group, namely a 1,3-propanediol moiety. As described above, there are specific advantages to the use of such a linking diol. These are not obtained with a 2,3-butanediol linking group, so one of

ordinary skill would not have been motivated to modify the 2,3-butanediol group of the '189 publication to obtain the 1,3-propanediol group of the present claims.

European publication no. 246,540 relates to implant preparations for bioactive macromolecules. The implant contains glycerides of various fatty acids, none of which correspond to the compounds of the present invention, either in the acid moieties or in the diol moiety. As explained above, the 1,3-diol moiety has specific, desirable properties as a linking moiety that are not possessed by a glycerol linking moiety. A worker having ordinary skill in the art would not have been motivated to modify both the linking moiety and the fatty acid moieties to obtain compounds of the present claims.

European publication no. 405,873 relates to edible fat replacements that may be long chain vicinal diol esters of fatty acids. However, the structural formula at page 3 of the '873 publication requires that A be an alkyl group having from 7 to 28 carbon atoms. Thus, even if one of ordinary skill in the art were to pick and choose from among the compounds disclosed in the '873 publication, and were to ignore the clear teachings in the reference to select a compound where n is 0, the result would still not be an adjacent homolog of the claimed compounds, but rather a compound having a long chain diol moiety. As pointed out repeatedly above, the 1,3-propane diol linking moiety provides specific desirable properties to the resulting compound. These are not obtained with the long chain linking moiety of the '873 publication. As a result, one of ordinary skill in the art would not have been motivated to modify the linking moiety of the '873 publication to remove the required long chain alkyl

group on the diol, and would not expect to obtain the advantages achieved with the present invention by using a 1,3-propanediol moiety.

Japanese publication no. 57-067511 relates to alkane-diol diesters of fatty acids used as agents for imparting iridescent luster to cosmetics. However, based upon the English language abstract of this publication, the disclosure of the fatty acids is no more specific than "13-23C straight-chain alkyl." There would have been no motivation for one of ordinary skill in the cosmetic art to select the specific unsaturated fatty acids recited in the present claims, since the '511 publication is concerned only with increasing molecular weight to obtain a high melting point, and not with obtaining therapeutic effects. Moreover, such a worker, reading the '511 abstract, would not have expected that the fatty acid esters of the present claims would possess therapeutic properties as described in the present specification.

Breusch et al. discloses 1,3-propanediol esters of fatty acids. However, the fatty acids are saturated, and Breusch et al., like the Japanese publication, appears to be primarily concerned with achieving a high molecular weight, and thus a high melting point, rather than with achieving any therapeutic effects. There would have been no motivation for one of ordinary skill in the art to modify the compounds disclosed in Breusch et al. to use the unsaturated fatty acids recited in the claims, which are found in high proportion in lipid membranes in the body.

In view of the above, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness over any of the 15 cited references, and that the rejection should accordingly be withdrawn.

B. Claims 27-35 and 39-41

At page 4 of the Office action, the Examiner has rejected claims 27-35 and 39-41 as obvious under 35 U.S.C. § 103(a) over Schaefer (U.S. Patent No. 5,321,145) or the British '762 publication, or European publications 184,058, or 222,155, or 246,540, or 321,128, or 393,920, or 405,873. Applicants respectfully traverse this rejection and request reconsideration and withdrawal thereof.

Again, Applicants assume that the Examiner is making this rejection over each of the eight (8) references individually, since there is no indication that any of the reference teachings are to be combined.

Schaefer relates to processes for producing phosphatidylcholine derivatives that are structurally very different from the presently claimed compounds, which do not include phosphate compounds. There would have been no motivation for one of ordinary skill in this art to modify the phosphatidylcholine derivatives of Schaefer so radically as to obtain the compounds of the present claims, because the structures are so diverse.

The British '762 publication has been described above, and does not render the claims obvious for the reasons set forth therein.

European publication 184,058 discloses indole derivatives that are structurally very different from the compounds of the present claims, which do not cover indole-containing fatty acid esters, nor esters of hydroxyacetic acid. Applicants have been unable to locate any portion of the '058 publication that even discloses a propandiol moiety, much less a disubstituted 1,3-propanediol moiety. Because of the numerous structural dissimilarities

between the compounds disclosed by the '058 publication and the claimed compounds, Applicants submit that a worker of ordinary skill in this art would not have been motivated to modify the '058 compounds to obtain the present invention.

The European '155 publication has been described above, and does not render the claimed invention obvious because a worker of ordinary skill in this art would not have been motivated to make the drastic structural modifications to the 5-fluorouracil compounds disclosed in the reference that would be necessary to obtain compounds falling within the present claims.

The European '540 publication has also been described above, and does not render the present claims obvious for the reasons set forth therein.

European publication 321,128 relates to the administration of a cyclosporin, a cyclic peptide, in conjunction with GLA or DGLA, or a derivative thereof (disclosed in the specification as glycerides, salts, esters, amides, or other pharmaceutically acceptable forms). No mention is made of the use of a 1,3-propanediol linking moiety between two fatty acid moieties or of the advantages that such a compound provides. Accordingly, one of ordinary skill in this art would not have been motivated to modify the disclosure of the '128 publication to obtain the present invention.

European publication 393,920 relates to antiviral nucleosides that may be derivatized with certain fatty acids. However, the present claims exclude such compounds, both because the recited substituents of the claims exclude nucleosides, and because the only linking

moiety disclosed in the '920 publication is an ethylene glycol moiety, not the 1,3-propanediol moiety recited by the present claims.

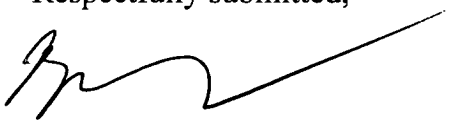
European publication no. 405,873 has been described above, and does not render the claimed invention obvious for the reasons set forth therein.

Based upon the above arguments, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness, and that this rejection should be withdrawn.

Applicants submit that the present claims are in condition for immediate allowance, and an early notification to that effect is earnestly solicited. If the Examiner believes that further issues remain to be resolved, he is respectfully requested to contact the undersigned at 404.815.6218 so that a telephonic interview can be arranged to dispose of said issues prior to the issuance of a final rejection.

Please charge any additional fees or credit any overpayment to Deposit Order Account No. 11-0855.

Respectfully submitted,



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